Case reports

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN AN HIV/TB CO-INFECTED PATIENT FOUR YEARS AFTER STARTING ANTIRETROVIRAL THERAPY

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ABSTRACT

The Immune reconstitution inflammatory syndrome (IRIS) after starting antiretroviral therapy for HIV is well known. We describe an HIV seropositive woman, presenting 2 IRIS episodes associated with Mycobacterium tuberculosis. Exceptional was that the last episode occurred 4 years after initiating antiretroviral treatment, when her CD4+ lymphocyte count had been around 300 cells/mm³ for one year.

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INTRODUCTION

The goal of Highly Active Antiretroviral Therapy (HAART) is to restore the immune system so as to prevent the development of opportunistic infections (OI). Immune restoration can go along with paradoxical clinical deterioration due to an over-vigorous immune-inflammatory reaction, known as Immune Reconstitution Inflammatory Syndrome (IRIS) (1). IRIS has been reported with *Mycobacterium tuberculosis* (TB), *Mycobacterium avium* complex, herpes viruses, cytomegalovirus, *Cryptococcus neoformans* and many other infectious and non-infectious diseases (2).

Some authors use the term "paradoxical reaction" instead of IRIS. While both terms describe a clinical worsening of TB, the term paradoxical reaction is generally used in the case of worsening TB disease, in both HIV-seronegative and -seropositive patients, after the initiation of anti-tuberculosis treatment, while the term IRIS is used in HIV-seropositive TB patients who have initiated HAART.

Though still uncertain, the pathogenesis of paradoxical reactions in HIV-seronegative TB patients might be explained by an increased immunological response by reactive lymphocytes and monocytes (3). During IRIS, the increased immunological response is enhanced not only by TB treatment, but also, potentially, by the reduction in viral load due to HAART.

Most cases of TB IRIS were reported in patients who had recently commenced HAART (4-7). One case oc-

curring one year (8) and another approximately two years after initiation of HAART have been reported (9). We describe here a patient who developed two episodes of TB IRIS, the first shortly after starting HAART, and the second nearly four years later. The first episode has been previously reported (10).

CASE REPORT

First TB IRIS episode

In February 2000, a 32-year-old Belgian woman, who had been living in Indonesia for years, was repatriated with wasting and chronic fever. She tested HIV-1 positive, having a plasma viral load of > 750,000 HIV-1 RNA copies/ml and a $CD4^+$ lymphocyte count of 19 cells/mm^3. HAART, consisting of stavudine, lamivudine and indinavir was initiated. Histological exam of liver and bone marrow biopsy demonstrated granulomatous lesions containing acid-fast bacilli (AFB), and the bone marrow aspirate culture revealed drug-sensitive *Mycobacterium tuberculosis*. Rifabutin (150 mg daily), pyrazinamide (1500 mg daily), isoniazid (300 mg daily), and ethambutol (1200 mg daily) were added 2 weeks after HAART initiation, with rapid resolution of the fever.

Two weeks later she developed TB IRIS with fever, generalised lymphadenopathy and subcutaneous abscesses. The latter were localized to the right upper arm, the thorax under the clavicle and the cervical area (figure 1). Because of persistent fever, HAART was interrupted, while TB treatment was continued. After a 2-week interruption of HAART, rifabutin was replaced with rifampicin, and stavudine, lamivudine and abacavir treatment was initiated. Over the next 9 months, abscesses and fever waxed and waned, usually improving temporarily with the administration of prednisone (32 mg/day), which was slowly tapered according to clinical symptoms, and finally disappeared completely. Though AFB were still found upon direct examination of the aspirate from abscesses 8 months after the start of anti-TB treatment, cultures remained negative.

In total, the patient completed 12 months of rifampicin, pyrazinamide, isoniazid, and ethambutol, although there were short interruptions in both TB treatment and HAART lasting a couple of days, due to therapy fatigue and digestive problems that were, according to the patient, provoked by the drugs.

Second TB IRIS episode

From 2001 on, treatment consisted of stavudine, didanosine and abacavir. During this time, the clinical condition of the patient remained excellent. In February 2003, tenofovir was added since her viral load was detectable. At the end of 2003, her $CD4^+$ lymphocyte counts had been around 300 cells/mm^3 (20%) for more than a year.

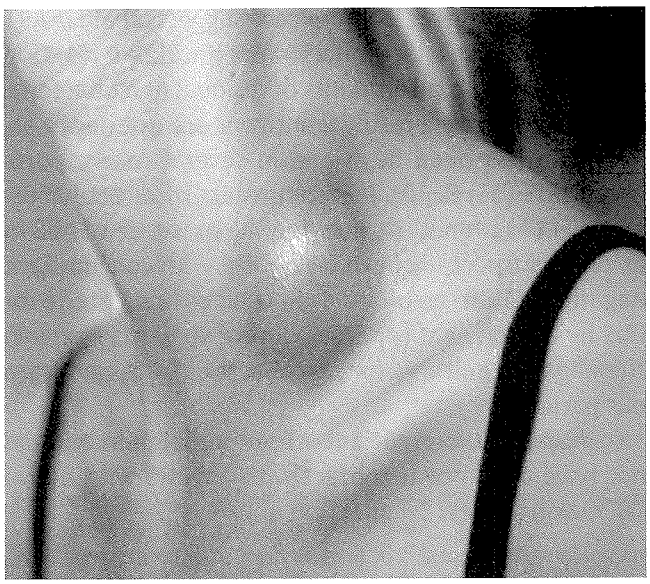

Figure 1: Cervical abscesses caused by TB IRIS weeks after initiation of HAART (as published in Acta Clinica Belgica in 2002)

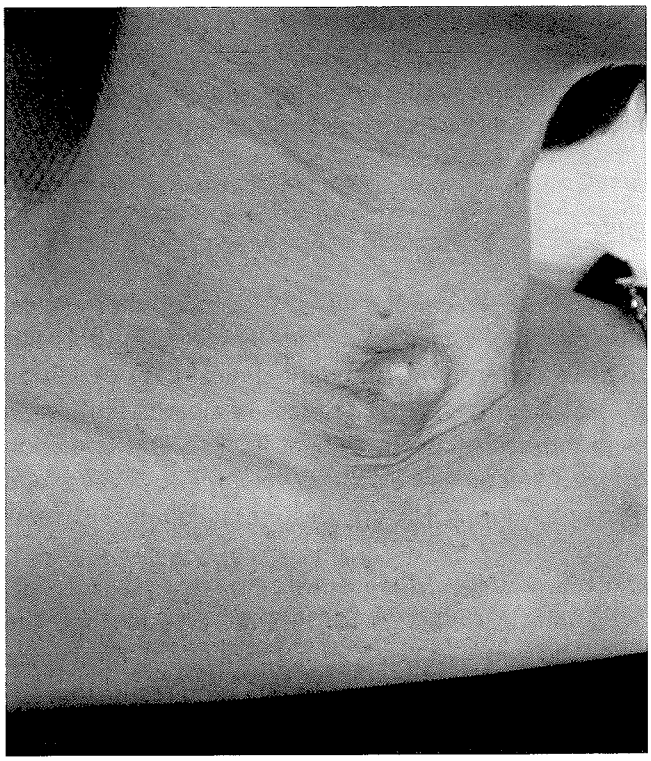

Figure 2: Almost identical clinical picture with cervical abscesses, now almost 4 years after the initiation of HAART, caused by late TB IRIS

In December 2003, after almost 4 years of HAART, she presented with fever and a cervical abscess (figure 2), unresponsive to treatment with amoxy-clavulanic acid. Ziehl-Neelsen staining on the aspirate yielded 2 AFB, although cultures remained negative. Her $CD4^+$ lymphocyte count was 292 cells/mm^3 and her viral load was undetectable. Rifabutin (300 mg), isoniazid (300 mg) and ciprofloxacin (500 mg bid) were started; ethambutol was a part of the treatment, but the patient refused to take it, because it made her nauseous. Two weeks later, the abscess drained spontaneously and the fever disappeared.

In February 2004, after 5 weeks of anti-TB treatment, she developed some swelling under the right clavicle and on the right upper arm. The ultrasound showed hypo-reflective areas in the right pectoral muscle and the *m. biceps brachii* (measuring respectively 44.2 x 21.3 mm and 45.7 x 13 mm). A computed tomography scan confirmed the lesions, and also demonstrated another abscess in the psoas muscle. At this time, her $CD4^+$ lymphocyte count was 300/mm^3 and her viral load was still undetectable.

She received 8 months of rifabutin, isoniazid and ciprofloxacin, while continuing HAART. In September 2004, her antiretroviral treatment, which had remained unchanged since the beginning of 2003, was switched to atazanavir, ritonavir, tenofovir, zidovudine and lamivudine. Since completion of her second episode of TB treatment she has remained asymptomatic.

DISCUSSION

IRIS is a clinical diagnosis. Suggestions for clinical case definitions have been made by several authors, but there is currently no standard clinical case definition (11). For late onset IRIS, the lack of clear definitions is even more obvious. In general, TB IRIS is a condition often characterized by the development of fever and abscesses during HAART, despite adequate TB treatment.

Laboratory markers for IRIS are also lacking. The value of increased levels of IL-6, soluble IL-6 receptor and soluble CD30 to identify IRIS requires further research (11).

The first episode of TB IRIS in our patient can be labelled as IRIS according to definitions that are currently used in the literature. Since the clinical presentation of the second episode was almost identical to the first, we suspected it was also due to an IRIS.

The pathogenesis of IRIS and TB IRIS in particular, remains poorly understood. It is generally thought to be the restoration of immune responses to antigens (viable or not), producing exuberant inflammatory reactions.

The early IRIS in our patient was probably caused by rapid changes in $CD4^+$ dynamics against a background of high bacillary burden. Known risk factors for TB IRIS, such as extra-pulmonary or disseminated disease, a low $CD4^+$ lymphocyte count (< 50 cells/mm^3) at the start of HAART, a viral load of > 10^5 $\log_{10}$ copies/ml and a good immunological and virological response during HAART (5;12-14), were all present at the moment she developed her first episode of TB IRIS.

The reason she developed a second episode of TB IRIS, in the presence of a stable $CD4^+$ lymphocyte count (fluctuating around 300/mm^3) and a very low mycobacterial load, is unclear.

Evidence of a stable blood $CD4^+$ count is not inconsistent with IRIS. Wilkinson *et al* demonstrated that blood $CD4^+$ counts may not reflect immune function at the locus of clinical deterioration, such as the lymph node. In non-HIV related TB, local antigen responses were found to be different from those detected in peripheral blood (15). Lipman *et al* also stressed the importance of measuring immune changes in the appropriate anatomical site (16) when assessing IRIS.

Though the typical early TB IRIS case is usually seen with a high antigenic load, our case suggests that HAART can also provoke a late inflammatory immune reaction in response to small amounts of residual mycobacteria. The fact that these residual antigens are not necessarily viable has been described in several case reports about IRIS (17, 8, 18). Positive results of direct bacteriological examination, showing the presence of AFB in an organ suspected of exhibiting IRIS, with concomitant negative culture results is even used as one criteria for IRIS by Breton *et al* (4). This point of view may explain the negative cultures for mycobacteria obtained from our patient.

Since 2000, our patient stayed in Belgium and did not have any known contact with anyone with active TB, making a new TB infection unlikely.

Informing patients with risk factors for IRIS in advance of the fact that this condition could occur might improve patient agreement and adherence to therapy.

Though most of the evidence supporting the use of corticosteroids for IRIS is from case reports and retrospective series where it was successfully used, and not from randomized controlled trials, it is generally strongly recommended to consider steroids for TB IRIS with abscesses and persistent fever, after ruling out conditions which can mimic IRIS (19). Adding or intensifying antimicrobial treatment may not be necessary in the case of late IRIS, where a non-viable antigen might be causing the clinical picture (1), and where the disease is of an inflammatory and possibly self-limiting nature. Our negative culture result for *M. tuberculosis* argues for the fact that the immune reaction was indeed directed against a persisting non-viable antigen. We opted, however, to administer TB treatment to our patient, since we could not exclude the presence of viable mycobacteria with absolute certainty. Moreover, our patient clearly improved with TB treatment.

ABSTRACT

Het immuun reconstitutie inflammatoir syndroom (IRIS) na opstarten van antiretrovirale therapie voor HIV is bekend. Wij rapporteren het geval van een HIV seropositieve patiënte die 2 IRIS episodes geassocieerd met *Mycobacterium tuberculosis* doormaakte. Uitzonderlijk is dat de tweede episode 4 jaar na het opstarten van de antiretrovirale therapie plaatsvond, met een $CD4^+$ lymfocyten telling die al een jaar rond de 300 cellen/mm^3 schommelde.

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